

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
24 October 2002 (24.10.2002)

PCT

(10) International Publication Number
WO 02/083637 A1

(51) International Patent Classification⁷: **C07D 207/34**,
405/06

PATEL, Pankaj, Ramanbhai [IN/IN]; Cadila Healthcare
Limited, 291, GIDC, Ankleshwar 393 002, Gujarat (IN).

(21) International Application Number: PCT/IN01/00110

(74) Agents: **SUBRAMANIAM, Hariharan** et al.; Subrama-
niam, Nataraj & Associates, Patent & Trademark Attor-
neys, E-556, Greater Kailash-II, New Dehli 110 048, Ma-
harashtra (IN).

(22) International Filing Date: 13 June 2001 (13.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
333/MUM/2001 11 April 2001 (11.04.2001) IN

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,
TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(71) Applicant (*for all designated States except US*): **CADILA
HEALTHCARE LIMITED** [IN/IN]; Zydus Tower, Satel-
lite Cross Roads, Amedadabad 380 015, Gujara (IN).

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **AGARWAL, Viren-
dra, Kumar** [IN/IN]; Cadila Healthcare Limited, 291,
GIDC, Ankleshwar 393 002, Gujarat (IN). **VAKIL, Man-
ish, Harshadbhai** [IN/IN]; Cadila Healthcare Limited,
291, GIDC, Ankleshwar 393 002, Gujarat (IN). **PANDITA,
Kanwal** [IN/IN]; Cadila Healthcare Limited, 291, GIDC,
Ankleshwar 393 002, Gujarat (IN). **RAMAKRISHNA,
Nirogi, Venakata, Satya** [IN/IN]; Cadila Healthcare
Limited, Zydus Research Centre, Sakhej Bavia N.H. No.
8A-Moraiya Village, Ahmedabad 382 213, Gujarat (IN).

Published:

— with international search report

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*



WO 02/083637 A1

(54) Title: PROCESS FOR THE PRODUCTION OF AMORPHOUS ATORVASTATIN CALCIUM

(57) Abstract: A process for the preparation of atorvastatin calcium in amorphous form is disclosed. The process comprises (i) treating diol protected tertbutyl ester with a methanolic solution in the presence of an aqueous acid; (ii) adding aqueous hydroxide solution to the reaction mixture; and removing unreacted diol protected tert-butyl ester (a) by solvent extraction (iii) treating the product obtained in step (ii) with calcium chloride solution to obtain crude amorphous atorvastatin calcium salt; (iv) isolating said crude salt; (v) treating the crude salt with excess volume of methanol; (vi) treating the product of step (v) with activated carbon and (vii) precipitation of the product by adding methanolic solution of atorvastatin calcium in to water (viii) recovering the pure product by filtration and drying.

EXPRESS MAIL NO. EV545395338US
DOCKET NO. PC25264A

PROCESS FOR THE PRODUCTION OF AMORPHOUS ATORVASTATIN CALCIUM

FIELD OF THE INVENTION

5

The present invention relates to a novel process for the production of atorvastatin calcium. Particularly, the present invention relates to a novel process for the production of amorphous atorvastatin calcium. More particularly, the present invention relates to a novel process for the production of amorphous atorvastatin calcium from a diol protected tert-butyl ester (a)

10

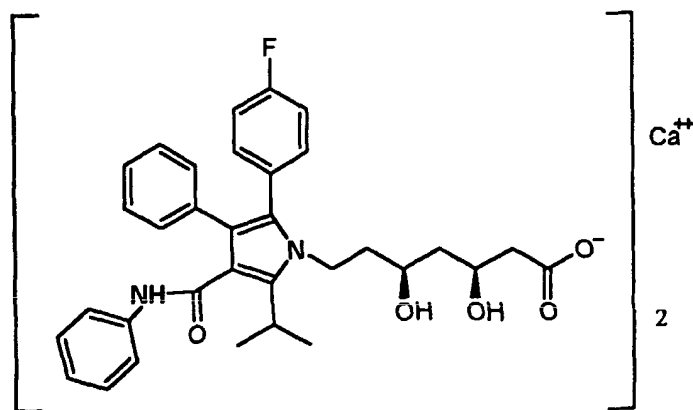
BACKGROUND OF THE INVENTION

Atorvastatin is chemically [R-(R*,R*)]-2-(4-FLUOROPHENYL)- β,δ -DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO) CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID. Atorvastatin calcium, a synthetic HMG-CoA reductase inhibitor, is used for the treatment of hyperlipidemia and hypercholesterolemia, both of which are risk factors for arteriosclerosis and coronary heart disease. Open dihydroxy carboxylic acid, lactone and various salt forms of atorvastatin have been synthesized.

15

According to the disclosure contained in the United States Patent 5,273,995, describes that R-form of the ring opened acid form has surprising inhibition of the biosynthesis of cholesterol. Atorvastatin in its calcium salt form, i.e. [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) having formula 1:

20



25

is more suited to formulations and has been recommended as a drug.

United states patents 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,273,995; 5,280,126; 5,298,627; 5,342,952; 5,385,929; 5,397,792; European Patent 409,281; and PCT publication No. 8,907,598 describe various processes and key intermediates for preparing
5 atorvastatin.

Atorvastatin is, preferably, prepared as its calcium salt, i.e. [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-
[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2 : 1) since
the calcium salt is desirable and it, enables easy formulation of atorvastatin for
10 example, tablets, capsules, lozenges, powder and the like for oral administration.

One of the major drawbacks of the prior art processes referred to above is that none of these processes consistently produce amorphous atorvastatin calcium but generally gives a mixture of its crystalline and amorphous forms with unsuitable filtration and drying characteristics, rendering them unsuitable
15 for large-scale production.

PCT application, WO 97/03958 and WO 97/03959 disclose novel crystalline forms of atorvastatin calcium designated as Form I, Form II, Form III and Form IV and method for their preparation which provide more favorable filtration and drying characteristics.

20 PCT application, WO 97/03960 and US Patent 6087511 describe the procedures for converting the crystalline form of atorvastatin calcium to the amorphous form. The process disclosed therein involve dissolving form I atorvastatin calcium in a non hydroxylic solvent like tetrahydrofuran or a mixture of tetrahydrofuran and toluene. None of these processes disclosed
25 therein is suitable for large scale production as solvent has to be removed at high temperature about 85 - 90°C and under high vacuum (5 - 10 mm of mercury) and the product thus obtained is in the form of a brittle glassy foam which has to be broken into a free flowing powder. The process disclosed therein also takes very long time for the removal of solvents

30 PCT application WO 00/71116 describes the procedure for converting the crystalline form-I by dissolving it in a non-hydroxylic solvent like tetrahydrofuran and precipitating amorphous atorvastatin calcium by the

addition of nonpolar hydrocarbon solvents like, n-hexane, cyclohexane or n-heptane. The method disclosed in this PCT application is not suitable for large scale production of amorphous atorvastatin calcium as the process requires very large amount of non polar hydrocarbon solvents, i.e about 20 – 40 times as that
5 of crystalline atorvastatin calcium and the mixture of tetrahydrofuran and non-polar hydrocarbon solvent obtained from the mother liquor would not be of any use for further recycling of the solvents. Secondly the solvents used therein have very low flash points (tetrahydrofuran → -17°C, n-hexane → -23°C, n-heptane → -1°C) making the process very unsafe on the commercial scale.

10 **Objects of the invention**

It is therefore, an object of the present invention to provide a process for the preparation of amorphous atorvastatin calcium which avoids all the disadvantages of the prior art

It is a further object of the present invention to provide a process for the
15 preparation of amorphous atorvastatin calcium consistently and which avoids production of a mixture of amorphous and crystalline forms.

It is yet another object of the present invention to provide a process for the preparation of amorphous atorvastatin calcium, which is economical and capable of being practiced on a commercial scale.

20 It is a further object of the present invention to provide a process for the conversion of crystalline atorvastatin calcium in to its amorphous form, which is economical and is capable of being practiced on a commercial scale.

Summary of the invention

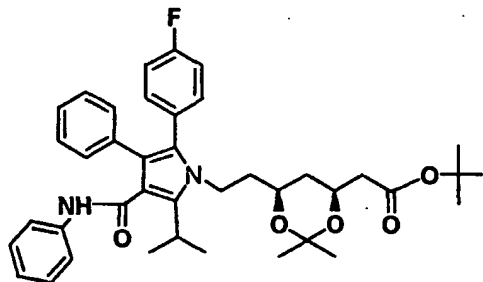
The above and other objects of the present invention are achieved by a
25 novel process for the preparation of amorphous form of atorvastatin calcium directly from the intermediate (4R-cis)-1,1-dimethylethyl-6-[2-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrol-1-yl]-ethyl]-2,2-dimethyl-1,3-dioxane-4-acetate, diol protected tert-butyl ester (a) which is an intermediate in the synthesis of atorvastatin lactone, a
30 starting material from which different polymorphs of atorvastatin calcium such as Form I and Form IV may be prepared. Similarly, preparation of Form II, Form III, and amorphous form by interconversion has been reported in the prior

arts. However, to the applicants' knowledge, not a single process is available to prepare amorphous form of atorvastatin calcium directly from the above mentioned intermediate (a), without employing corresponding lactone compound. Accordingly, the present invention discloses a novel process for the preparation of amorphous atorvastatin calcium from the above mentioned intermediate (a) on commercial scale, while in earlier prior arts, crystalline form - I of atorvastatin calcium is employed for the preparation of amorphous atorvastatin calcium. The present invention also discloses a novel process of converting form - I of atorvastatin calcium into amorphous form, which is suitable for converting all the crystalline forms of atorvastatin calcium in to amorphous form on commercial scale.

Detailed description

The process of the present invention eliminates the problems of prior arts. The present invention also discloses for the first time a process of manufacturing amorphous atorvastatin calcium directly from diol protected tert-butyl ester (a). The crude stage may contain some amount of calcium hydroxide which is easily removed completely in the subsequent purification stage. At both the stages of preparation, atorvastatin calcium prepared by the process of the present invention was found to be amorphous as revealed by X-ray powder diffraction data (figure -1 & 2). The present invention does not make use of any crystalline form to get amorphous atorvastatin calcium like other prior arts. However conversion of form- 1 of atorvastatin calcium in to amorphous atorvastatin calcium disclosed herein is an additional procedure within the scope of the present invention to exploit on commercial scale and does not in any way deviate from the basic purpose of this invention of getting amorphous atorvastatin calcium without employing any crystalline form. In the present invention, purification stage of atorvastatin calcium is conveniently used to convert crystalline forms of atorvastatin calcium into amorphous atorvastatin calcium. The present invention does not employ corresponding lactone compound to convert it into atorvastatin calcium like other prior arts. The present invention makes the use of relatively safer solvent i.e. methanol with higher flash point $\rightarrow +11^{\circ}\text{C}$.

Accordingly, the present invention provides a process for the preparation of atorvastatin calcium in amorphous form which comprises treating diol protected tert-butyl ester of following structure (a) below



(a)

with a methanolic solution in the presence of a dilute acid and subsequently treating the reaction mixture with dilute hydroxide solution and then with dilute calcium chloride solutions to obtain a white slurry of the material in the solution, removing the material from the solution to obtain crude amorphous atorvastatin calcium and purifying said crude amorphous atorvastatin calcium to obtain pure amorphous atorvastatin calcium. Preferably, the crude material is removed from the solution centrifuging the solution and drying the product so obtained at 50 – 60 °C for several hours till water content 4 – 6% is achieved. The crude amorphous atorvastatin calcium so obtained contains some amount of calcium hydroxide formed during the reaction of calcium chloride with free sodium hydroxide present in the reaction mixture. The crude material is purified by dissolving it in methanol (10% w/v) giving opalescence due to calcium hydroxide. Preferably, the crude material is dissolved in methanol at 30 – 35 °C (10% w/v) and treated with activated carbon and filtered through hyflow bed over nutsch filter. The clear solution thus obtained is again filtered through 5-micron candle filter to get absolutely clear and transparent methanolic solution of atorvastatin calcium. This solution is added slowly to fine filtered D.M.Water at 50 – 55°C (the amount of water is taken twice as that of methanolic solution v/v), resulting in the free flowing precipitation of pure amorphous atorvastatin calcium with normal agitation (70 rpm) which is cooled to 10 – 15°C and then centrifuged and dried at 50 – 60°C for several hours till water content 4 – 6% is achieved.

Preferably, the aqueous acid is selected from hydrochloric acid , sulphuric acid , and formic acid; aqueous hydrochloric acid is being most preferred. The aqueous hydroxide solution is selected from sodium hydroxide, potassium hydroxide, and lithium hydroxide. In a most preferred embodiment, aqueous sodium hydroxide is employed.

In another preferred embodiment, the crude salt as well as the purified products are isolated by filtration and then dried.

In another preferred embodiment, the diol protected tert-butyl ester of the structure (a) is treated with 20 - 40 times w/v methanol. More preferably, the amount of methanol employed is 28 times w/v.

The HCl employed is preferably 2 -6% aqueous w/v, more preferably 4% w/v in a molar ratio of 1.5 - 4, preferably 2.0. The reaction temperature is preferably maintained at a range of from 20-40°C preferably, 30 -35°C for 8 - 20 hours preferably for 15 hours.

In another preferred embodiment, the dilute aqueous sodium hydroxide solution employed ranges from 5 - 20% w/v, preferably 10% w/v in molar ratio of 1 - 1.5, more preferably, 1.35, (after calculating the amount of sodium hydroxide required for neutralization of hydrochloric acid present in the reaction mixture). The reaction mass is stirred for 2 - 6 hours, preferably, for 5 hours

The pH of the reaction mixture is preferably maintained 7.0 - 9.5, more preferably 8.5 by addition of 4% w/v aqueous hydrochloric acid. In preferred embodiment, pH is always maintained at a level > 7.0.

The aqueous calcium chloride solution is preferably employed in the range of 2 - 6% w/v preferably 4 - 5 % in the molar ratio of 1 - 2, more preferably 1.65. The reaction temperature is maintained at a temperature in the range of 50 - 55°C for 15 - 60 minutes preferably for 60 minutes.

The precipitated material is preferably cooled to 25 - 40°C, more preferably to 30 - 35°C, which is further cooled to 0 - 20°C preferably, to 10 - 15°C. The stirring is continued for 30 - 120 minutes preferably, for 60 minutes at

10 - 15°C The material is centrifuged easily and is preferably washed with D.M.Water to remove excess calcium chloride.

The present invention describes the method of converting diol protected tert-butyl ester (a) of atorvastatin directly into crude amorphous atorvastatin calcium which contains some amount of calcium hydroxide which is removed in subsequent purification step. The whole process consists of following key operations

1) Treating of diol protected tert-butyl ester (a, scheme - 1) in methanol 20 - 40 w/v times methanol, as that of diol protected tert-butyl ester, preferably 28 times with 2 - 6% aqueous w/v hydrochloric acid preferably 4% w/v hydrochloric acid solution in a molar ratio of 1.5 - 4 preferably 2.0 at the temperature range of 20-40°C preferably at 30 - 35°C for 8 - 20 hours preferably for 15 hours. HPLC analysis of reaction mixture after 15 hours shows the presence of unreacted diol protected tert-butyl ester (a) (0.56%), as in scheme - 1. HPLC analysis also shows formation of 4 intermediates (b,c,d and e) as shown in scheme - 1 with distribution pattern as follows. This is an illustrative pattern. The percentage and distribution may vary depending on the reaction conditions.

(i)	atorvastatin diol tert-butyl ester (b)	-	72.00%
(ii)	atorvastatin diol methyl ester (c)	-	21.16%
(iii)	atorvastatin lactone (d)	-	2.52%
(iv)	atorvastatin diol acid (e)	-	0.96%

2) The above solution is treated with dilute aqueous sodium hydroxide solution ranging from 5 - 20% w/v preferably 10% w/v in molar ratio of 1 - 1.5 preferably 1.35 (after calculating the amount of sodium hydroxide required for neutralization of hydrochloric acid present in the reaction mixture). The reaction mass is stirred for 2 - 6 hours preferably for 5 hours when HPLC analysis shows the complete conversion of all the intermediates (b,c,d,and e) as mentioned in scheme - 1 into a single product, atorvastatin sodium (f) in the solution.

3) pH of the reaction mixture is adjusted between 7.0 - 9.5, preferably 8.5 by addition of 4% w/v aqueous hydrochloric acid, pH lower than 7.0 results in

the formation of lactone compound (d) in the final product, this also results in the decrease of the calcium content below the required amount i.e. 3.50 % w/w on dry basis.

- 4) The volume of the reaction mixture is then reduced to approximately 50% by distillation under reduced pressure below 60°C
- 5) The volume of the reaction mixture is measured and the content of methanol and water are determined v/v.
- 6) The volume of the reaction mixture is then adjusted so that it contains 5 -15 times, preferably 10 times methanol and 5 - 10 times, preferably 7 times water with respect to diol protected tert-butyl ester (a) initially taken.
- 7) The reaction mixture is then washed with 5 - 15 times preferably 10 times as that of diol protected tert-butyl ester (a) taken for reaction with organic solvents insoluble in water such as toluene, xylene, diisopropyl ether, diethyl ether, dichloromethane preferably diisopropyl ether to remove starting material i.e. unreacted diol protected tert-butyl ester (a) from the reaction mixture.
- 8) Aqueous methanolic layer after extraction with diisopropyl ether is charged into another S.S.Reactor, finally pH is checked and if necessary, is adjusted to 8.5, the reaction mixture is heated to 40 - 60°C preferably to 50 - 55°C.
- 9) Aqueous calcium chloride solution in the range of 2 - 6% w/v preferably 4 - 5% in the molar ratio of 1 - 2 preferably 1.65 is added during 30 - 90 minutes preferably 60 minutes at 50 - 55°C with the smooth and uniform precipitation of atorvastatin calcium. If mode of addition is reversed, a sticky material is obtained under similar condition of operations.
- 10) The precipitated material is stirred at 50 - 55°C for 15 - 60 minutes preferably for 60 minutes.
- 11) The precipitated material is cooled to 25 - 40°C preferably to 30 - 35°C, which is further cooled to 0 - 20°C preferably to 10 - 15°C.
- 12) The stirring is continued for 30 - 120 minutes preferably for 60 minutes at 10 - 15°C

- 13) The material is centrifuged easily and is washed with D.M. Water to remove excess calcium chloride.
- 14) The wet cake of crude amorphous atorvastatin calcium which is 3 - 4 times as that of dried material is dried in a vacuum dryer at 40 - 70°C preferably at 50 - 60°C for several hours preferably for 8 - 10 hours till the water content in the range of 2 - 8% preferably 4 - 6% is achieved.
- 15) The dried material was found to contain traces of calcium hydroxide which is formed during the calcium chloride addition (excess sodium hydroxide in the reaction mixture reacts with calcium chloride to produce calcium hydroxide) which is insoluble in water and hence can not be removed even washing with plenty of D.M. Water. The next operations afterwards are being carried out to remove calcium hydroxide present in the crude amorphous atorvastatin calcium.
- 16) X-Ray powder diffraction study shows crude atorvastatin calcium to be amorphous (Fig. - 1).
- 17) Crude amorphous atorvastatin calcium is dissolved in methanol at 30 - 60°C preferably at 30 - 35°C in 5 - 15 times in volume preferably 7 times in volume as that of crude atorvastatin calcium and treated with activated carbon 2 - 10% w/w preferably 5% w/w at 30 - 35°C for 15 - 60 minutes preferably for 30 minutes.
- 18) Methanolic solution of atorvastatin calcium is then filtered through hyflow bed contained in a nutsche filter under vacuum and the bed is washed with fresh methanol.
- 19) The solution is finally filtered through 5 micron candle filter to get absolutely clear and transparent solution, free from any suspended particles. The filtration stages (18) and (19) completely remove calcium hydroxide present in the crude product.
- 20) The final volume of methanolic atorvastatin calcium is adjusted to 8 - 12 times in volume preferably 10 times in volume as that of crude atorvastatin calcium by addition of fine filtered methanol.

- 21) In another S.S.Reactor D.M.Water is charged 1 - 3 times preferably 2 times in volume as that of methanolic solution of atorvastatin calcium through 5 micron candle filter which is heated to 40 - 60°C preferably to 50- 55°C.
- 22) Methanolic solution of atorvastatin calcium is added slowly during 15 - 60 minutes preferably in 30 minutes at 50 - 55°C with free flowing and uniform formation of amorphous atorvastatin calcium in the reactor.
- 23) The precipitated material is stirred at 50 - 55°C for 10 - 40 minutes preferably for 20 - 30 minutes.
- 24) The precipitated material is cooled to 25 - 40°C preferably to 30 - 35°C which is further cooled to 0 - 20°C preferably to 10 - 15°C.
- 25) The stirring is continued for 30 - 120 minutes preferably for 60 minutes at 10 - 15°C
- 26) The material is centrifuged easily and is washed with plenty of D.M.Water.
- 27) The wet cake of pure amorphous atorvastatin calcium which is 3 - 4 times in weight as that of dried material is dried in a vacuum dryer at 40 - 80°C preferably at 50 - 60°C for several hours preferably for 8 - 10 hours till the water content in the range of 2 - 8% preferably 4 - 6% is achieved.
- 28) X-Ray powder diffraction study shows pure atorvastatin calcium to be amorphous and the product is free from calcium hydroxide.
- 20 Major advantages of the present invention compared to the prior art processes are:-
1. Direct conversion of diol protected tert-butyl ester (a, scheme - 1) into amorphous atorvastatin calcium in a hydroxylic solvents without preparation and isolation of lactone compound.
 - 25 2. Purification stage removes calcium hydroxide present in atorvastatin calcium completely.
 3. Crystalline forms of atorvastatin calcium are conveniently converted into amorphous atorvastatin calcium using purification procedures disclosed herein exemplified by conversion of form - I of atorvastatin calcium in to amorphous atorvastatin calcium.
 - 30 4. The process disclosed herein requires no high agitation or vigorous stirring like prior arts.

5. Avoiding the need to remove the solvent at higher temperature and under high vacuum.
6. Avoiding the need of using the solvents with lower flash points like tetrahydrofuran, n-hexane and n-heptane
- 5 7. Avoiding the need of using an uneconomical solvent like tetrahydrofuran.
8. Avoiding the need of recycling and separating a mixture of solvents obtained from mother liquor.
9. The process disclosed herein employs only one solvent in the manufacturing process i.e methanol that can be easily recovered, and
10 recycled. The process disclosed herein produces amorphous product consistently on commercial scale with allowable limits of residual solvent (methanol \rightarrow 500 - 1000 ppm)
10. The process disclosed herein is carried out by using relatively safer solvent (methanol) with flash point of $+11^{\circ}\text{C}$.
- 15 11. The process disclosed herein gives amorphous form directly without interconversion of any crystalline form into amorphous form.

The present invention will now be described in greater detail with reference to the accompanying drawings and examples in which

20 Figure 1 depicts X-ray powder diffractogram of amorphous atorvastatin calcium crude. The horizontal axis presents 2θ and the vertical axis corresponds to peak intensity.

Figure 2 shows X-ray powder diffractogram of amorphous atorvastatin calcium
pure. The horizontal axis presents 2θ and the vertical axis
25 corresponds to peak intensity.

Figure 3 shows X-ray powder diffractogram of form - I of atorvastatin calcium. The
horizontal axis presents 2θ and the vertical axis corresponds
to peak intensity.

30 Figure 4 illustrates X-ray powder diffractogram of amorphous atorvastatin calcium prepared by converting form - I of atorvastatin

calcium. The horizontal axis presents 2θ and the vertical axis corresponds to peak intensity.

Scheme 1 describes Schematic representation and distribution of the intermediates formed during the treatment of methanolic solution of diol protected tert-butyl ester (a) with dilute hydrochloric acid and subsequent conversion of all the intermediates into a single product atorvastatin sodium and then to atorvastatin calcium.

The present invention will now be illustrated by the following examples, which are not intended to limit the effective scope of the claims. Consequently, any variations of the invention described above are not to be regarded as departure from the spirit and scope of the invention as claimed. The present invention has been described in terms of its specific embodiments and various modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of present invention.

Example 1

[R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H pyrrole-1-heptanoic acid hemicalcium salt (Crude amorphous atorvastatin calcium).

20 Kg. of diol protected tert-butyl ester (a) is suspended in 560 lt. methanol in GLR and treated with 55 lt. of 4% aqueous w/v hydrochloric acid for 15 hours at 30 - 35°C then a solution of 4 Kg. sodium hydroxide in 40 lt. D.M.Water is added in 1 hour and stirring is continued for 5 hours. The pH of reaction mixture is adjusted to 8.5 by addition of 1 lt. of 4% w/v aqueous hydrochloric acid. The volume of the reaction mixture is reduced to approximately 50% by distilling below 60°C under vacuum (distilled volume 270 - 275 lt.). the analysis of the contents left behind in the reactor shows water content to be 83 lt. and methanol content to be 178 lt. Then 23 lt. methanol and 57 lt. water are added to the reaction mixture, reaction mixture is washed with 200 lt. of diisopropylether. Aqueous methanolic solution containing atorvastatin sodium is charged into another S.S.Reactor and finally pH is checked and if necessary adjusted to 8.5 and the contents are heated to 50 - 55°C to which a

aqueous solution of 2.8 Kg. calcium chloride in 60 lt. water is added in 1 hour at 50 - 55°C with the precipitation of atorvastatin calcium, the precipitated mass is stirred for 1 hr at 50 - 55°C which is cooled to 30 - 35°C (within 60 minutes), then cooled to 10 - 15°C (within 60 minutes), the precipitated material is further stirred for 1 hr at 10 - 15°C. The solid material is centrifuged and washed with D.M.Water. (Wet weight = 55 - 60 Kg.) The material is dried at 50 - 60°C for 8 hours till water content 4 - 6% is achieved giving 17.50 Kg. crude amorphous atorvastatin calcium. X-ray powder diffraction data confirmed the amorphous nature of the product.(Fig-1).

10

Example 2

The example disclosed herein is a purification stage in which calcium hydroxide in atorvastatin calcium is being removed.

17.0 Kg. crude amorphous atorvastatin calcium so obtained in example 1 is dissolved in 120 Lt. methanol and 0.85 Kg. activated carbon is added and stirred at 30 - 35°C for 30 minutes. Methanolic solution of atorvastatin calcium is filtered through hyflow bed over nutsche filter and washed with 20 lt. methanol. Filtered methanolic solution is passed through 5 micron candle filter, and the volume of this solution is adjusted to 170 lt. by addition of fresh fine filtered methanol. In another S.S.Reactor 340 lt. D.M.Water is taken through 5 micron candle filter and heated to 50 - 55°C, filtered methanolic solution of atorvastatin calcium is added in 30 minutes at 50 - 55°C in the reactor containing water with precipitation of pure atorvastatin calcium, which is stirred for another 20 minutes, at 50 - 55°C, the contents in reactor are cooled to 30 - 35°C (within 90 minutes) then cooled to 10 - 15°C (within 2 hours), the precipitated material is further stirred at 10 - 15°C for 1 hour. Pure amorphous atorvastatin calcium is centrifuged and washed with 40 lt. D.M.Water. (Wet weight = 45 - 50 Kg.) The material is dried at 50 - 60°C for 8 hours till water content 4 - 6% is achieved to give dry weight of 15 Kg. of pure amorphous atorvastatin calcium. X-ray powder diffraction data confirmed the amorphous nature of the product and the material thus obtained is free from calcium hydroxide.

30

Example 3

The example disclosed herein is a convenient procedure to convert crystalline forms of atorvastatin calcium in to amorphous atorvastatin calcium, exemplified here by converting form - I of atorvastatin calcium in to amorphous form.

5 20 gm atorvastatin calcium form - I (figure 3) is dissolved in 160 ml methanol at 45 - 50°C and then is treated with 2 gm activated carbon for 15 minutes at 45 - 50°C. the solution is cooled to 25 -35°C and is filtered through hyflow bed with 2 x 20 ml methanol wash. The volume of filtrate is adjusted to 200 ml by addition of fresh methanol. Finally filtrate is passed through 5 micron
10 filter pad to get absolutely clear and transparent solution of atorvastatin calcium in methanol. The methanolic solution of atorvastatin calcium is added to 400 ml of fine filtered D.M.Water at 50 - 55°C in 30 minutes. with stirring, resulting in the precipitation of atorvastatin calcium, stirring is continued for another 30 minutes at 50 - 55°C. The precipitated material is cooled to 30 - 35°C then to 10 -
15 15°C stirring is continued for 1 hr at 10 -15°C The material is filtered and washed with 2 x 50 ml of D.M.Water, dried at 50 -60°C for 8 hours till the water content 4 - 6 % is achieved, giving 18.0 gm dried atorvastatin calcium. X-ray powder diffraction data suggests the material to be amorphous (figure 4)

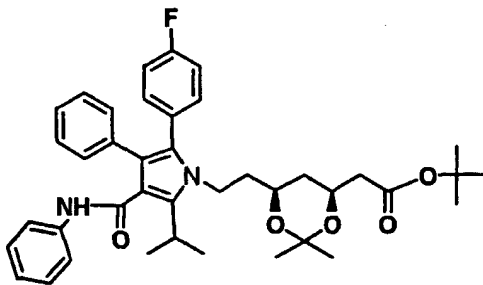
20

25

30

CLAIMS :-

1. A process for the preparation of atorvastatin calcium in amorphous form which comprises (i) treating diol protected tert-butyl ester of the following structure (a)



5

(a)

with a methanolic solution in the presence of an aqueous acid; (ii) adding aqueous hydroxide solution to the reaction mixture; and removing unreacted diol protected tert-butyl ester (a) by solvent extraction (iii) treating the product obtained in step (ii) with calcium chloride solution to obtain crude amorphous atorvastatin calcium salt; (iv) isolating said crude salt; (v) treating the crude salt with excess volume of methanol; (vi) treating the product of step (v) with activated carbon and (vii) precipitation of the product by adding methanolic solution of atorvastatin calcium in to water (viii) recovering the pure product by filtration and drying.

2. A process as claimed in claim 1 wherein said the aqueous acid is selected from hydrochloric acid, sulfuric acid and formic acid.
3. A process as claimed in claim 2 wherein said aqueous acid is aqueous hydrochloric acid.
4. A process as claimed in claim any one of claims 1 to 3 wherein said aqueous hydroxide solution is selected from sodium hydroxide, potassium hydroxide and lithium hydroxide
5. A process as claimed in claim 4 wherein said aqueous hydroxide employed is dilute aqueous sodium hydroxide.
6. A process as claimed in any preceding claim wherein the said crude salt as well as the purified products are isolated by filtration and then dried.

25

7. A process as claimed in any preceding claim wherein said diol protected tert-butyl ester (a) is treated with 20 - 40 times w/v methanol as that of compound (a) taken for reaction.
- 5 8. A process as claimed in claim 7 wherein said amount of methanol is 28 times w/v is that of compound (a) taken for reaction
9. A process as claimed in any preceding claim wherein said hydrochloric acid employed is 2 -6% aqueous w/v.
- 10 10. A process as claimed in claim 9 wherein said hydrochloric acid is 4% w/v.
11. A process as claimed in claim 9 or 10 wherein said hydrochloric acid employed is in a molar ratio of from 1.5 - 4.
12. A process as claimed in claim 11 wherein said molar ratio is 2.0.
13. A process as claimed in claim 1 wherein the reaction temperature is
15 maintained at range of from 20-40°C.
14. A process as claimed in claim 13 wherein said reaction temperature is 30 - 35°C.
15. A process as claimed in claim 1 wherein said reaction is carried out for 8 - 20 hours.
- 20 16. A process as claimed in claim 15 wherein said reaction time is 15 hours.
17. A process as claimed in claim 1 wherein four products (b,c,d, and e) as shown in scheme -1 are formed in a mixture in varying proportions on the treatment of methanolic solution of protected diol tert-butyl ester (a) with aqueous hydrochloric acid and intermediates (b,c,d, and e) thus formed
25 are converted into a single product atorvastatin sodium (f) in solution with the subsequent treatment of sodium hydroxide.
18. A process as claimed in claim any one of claims 5 to 16 wherein said dilute aqueous sodium hydroxide solution employed ranges from 5 - 20%
30 w/v.
19. A process as claimed in claim 18 wherein said dilute sodium hydroxide solution employed is in a molar ratio of 1 - 1.5 (after calculating the

amount of sodium hydroxide required for neutralization of hydrochloric acid present in the reaction mixture).

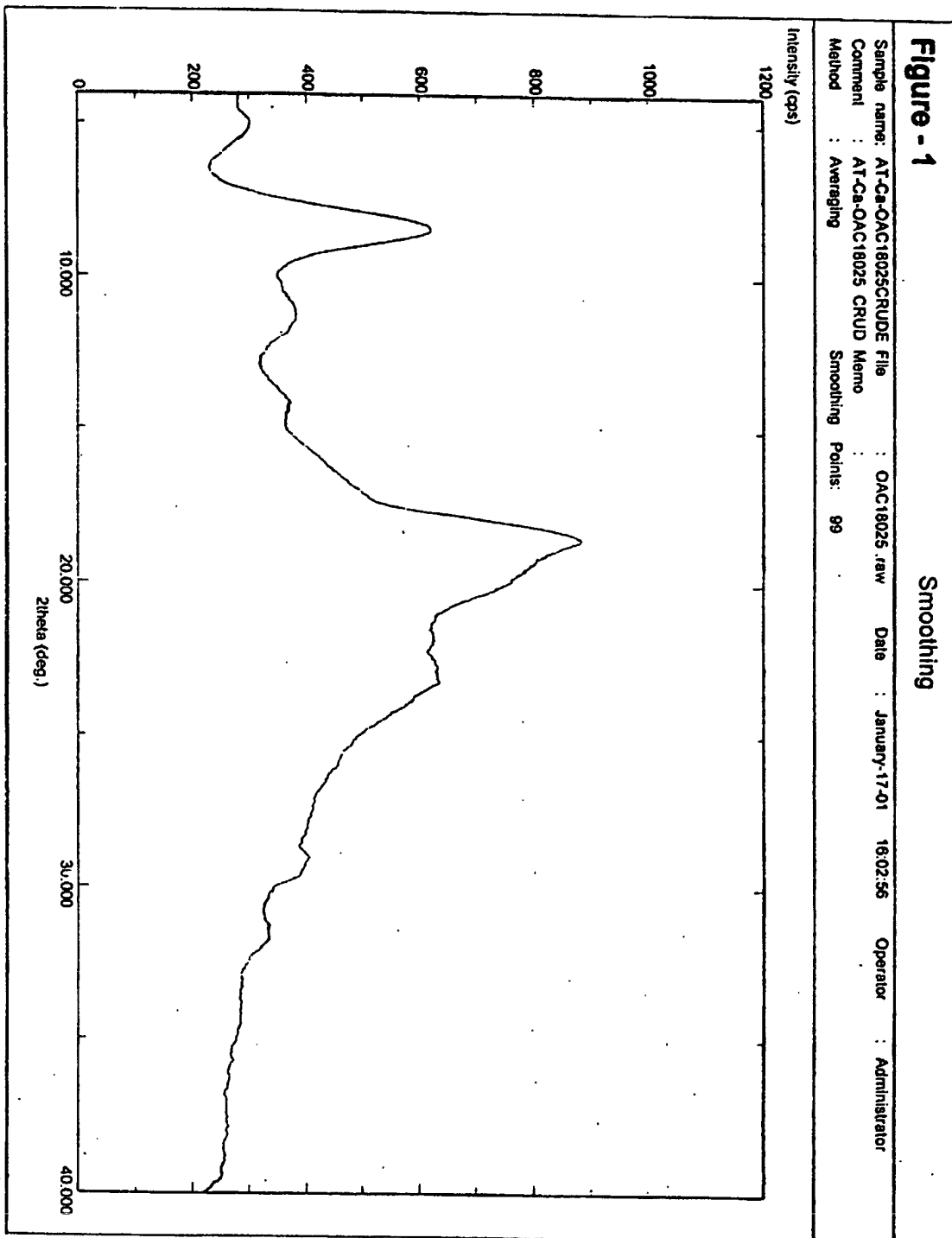
20. A process as claimed in claim 19 wherein said molar ratio is 1.35, (after calculating the amount of sodium hydroxide required for neutralization of hydrochloric acid present in the reaction mixture).
21. A process as claimed in claim 1 wherein in step (ii) the reaction mass is stirred for 2 - 6 hours.
22. A process as claimed in claim 21 wherein said reaction mass is stirred for 5 hours.
23. A process as claimed in claim 1 wherein the pH of the reaction mixture is maintained in the range of 7.0 - 9.5.
24. A process as claimed in claim 23 wherein said pH is 8.5.
25. A process as claimed in claim 24 wherein said pH of 8.5 is achieved by the addition of 4% w/v aqueous hydrochloric acid.
26. A process as claimed in claim 1 wherein said aqueous calcium chloride solution employed is in the range of 2 - 6% w/v.
27. A process as claimed in claim 26 wherein said aqueous calcium chloride solution employed is in the range of 4 - 5 %.
28. A process as claimed in claim 26 or 27 wherein said aqueous calcium chloride solution employed is in a molar ratio of 1 - 2.
29. A process as claimed in claim 28 wherein said molar ratio is 1.65.
30. A process as claimed in claim 1 wherein after the addition of aqueous calcium chloride, the reaction temperature is maintained in the range of 50 - 55°C for 15 - 60 minutes.
31. A process as claimed in claim 1 wherein unreacted diol protected tert-butyl ester (a) present in the reaction mixture is removed by solvent extraction.
32. A process as claimed in claim 31 wherein the solvent employed is selected from toluene, xylene, diisopropyl ether, diethyl ether and dichloromethane to remove protected diol tert-butyl ester-butyl ester (a) present in the reaction mixture.

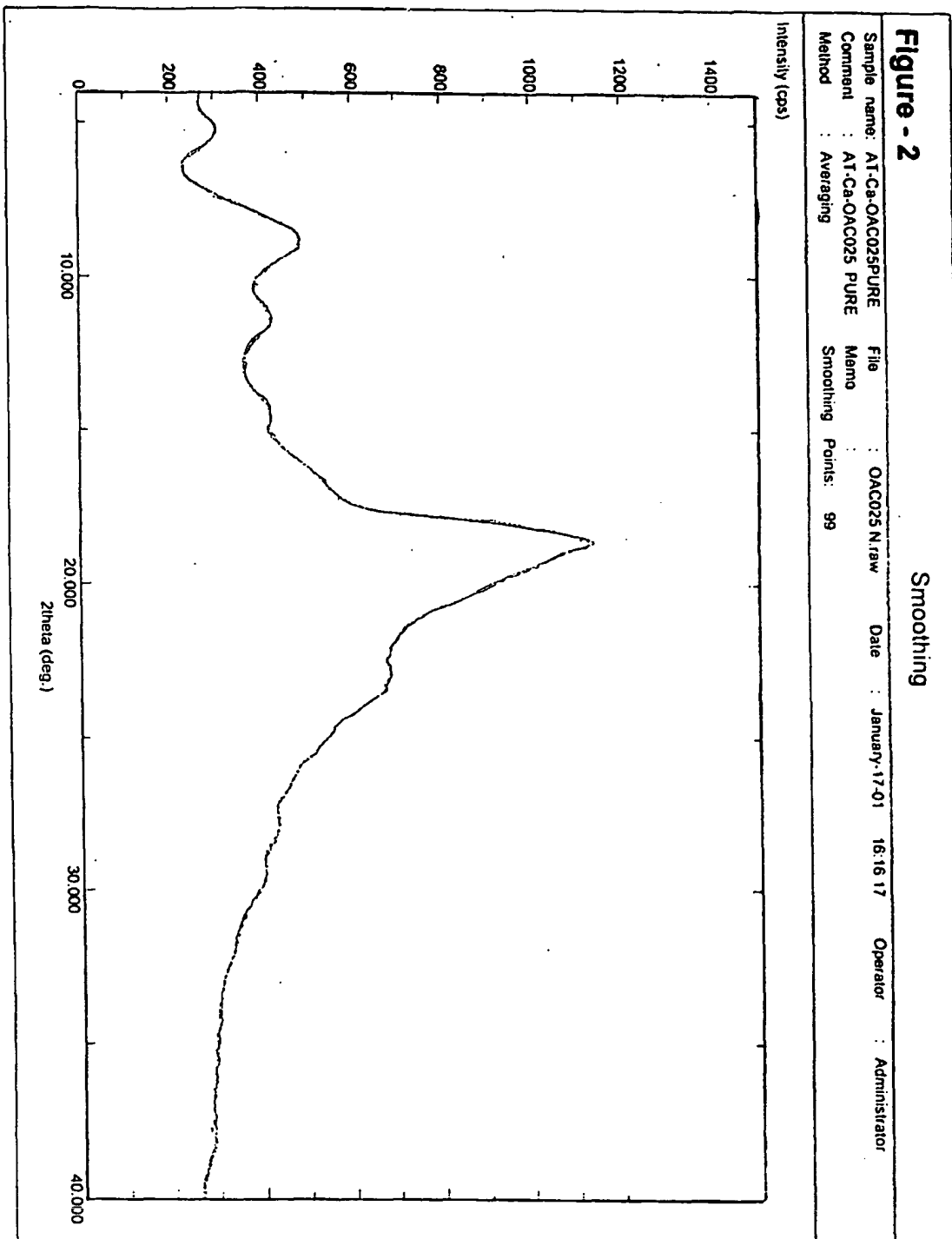
33. A process as claimed in claim 31 and 32 wherein the solvent employed is di-isopropyl ether.
34. A process as claimed in any preceding claim wherein the percentage of methanol in aqueous methanolic solution of atorvastatin sodium before the addition of aqueous solution of calcium chloride is 30 - 80% v/v.
35. A process is claimed in claim 34 wherein the percentage of methanol in aqueous methanolic solution of atorvastatin sodium before the addition of aqueous solution of calcium chloride is 60 % v/v.
36. A process as claimed in claim 1 wherein methanol is 7 - 15 times as that of protected diol tert-butyl ester-butyl ester (a) before the addition of aqueous calcium chloride solution to precipitate crude atorvastatin calcium.
37. A process as claimed in claim 36 wherein methanol is 10 times as that of protected diol tert-butyl ester-butyl ester (a) before the addition of aqueous calcium chloride solution to precipitate crude atorvastatin calcium.
38. A process as claimed in claim 1 wherein water employed is 5- 15 times as that of protected diol tert-butyl ester-butyl ester (a) before the addition of aqueous calcium chloride to precipitate crude atorvastatin calcium.
39. A process as claimed in claim 38 wherein water employed is 7 times as that of protected diol tert-butyl ester (a) before the addition of aqueous calcium chloride to precipitate crude atorvastatin calcium.
40. A process as claimed in claim 1 wherein the amount of methanol employed in step (v) is 5 to 15 times the volume of the crude salt treated.
41. A process as claimed in claim 40 wherein the amount of methanol employed is 7 times the volume of the crude salt treated.
42. The process as claimed in claim 1 wherein the volume of methanolic solution of crude amorphous atorvastatin calcium is 7 - 15 times as that of crude amorphous atorvastatin calcium before the methanolic solution is added to water to precipitate pure amorphous atorvastatin calcium.

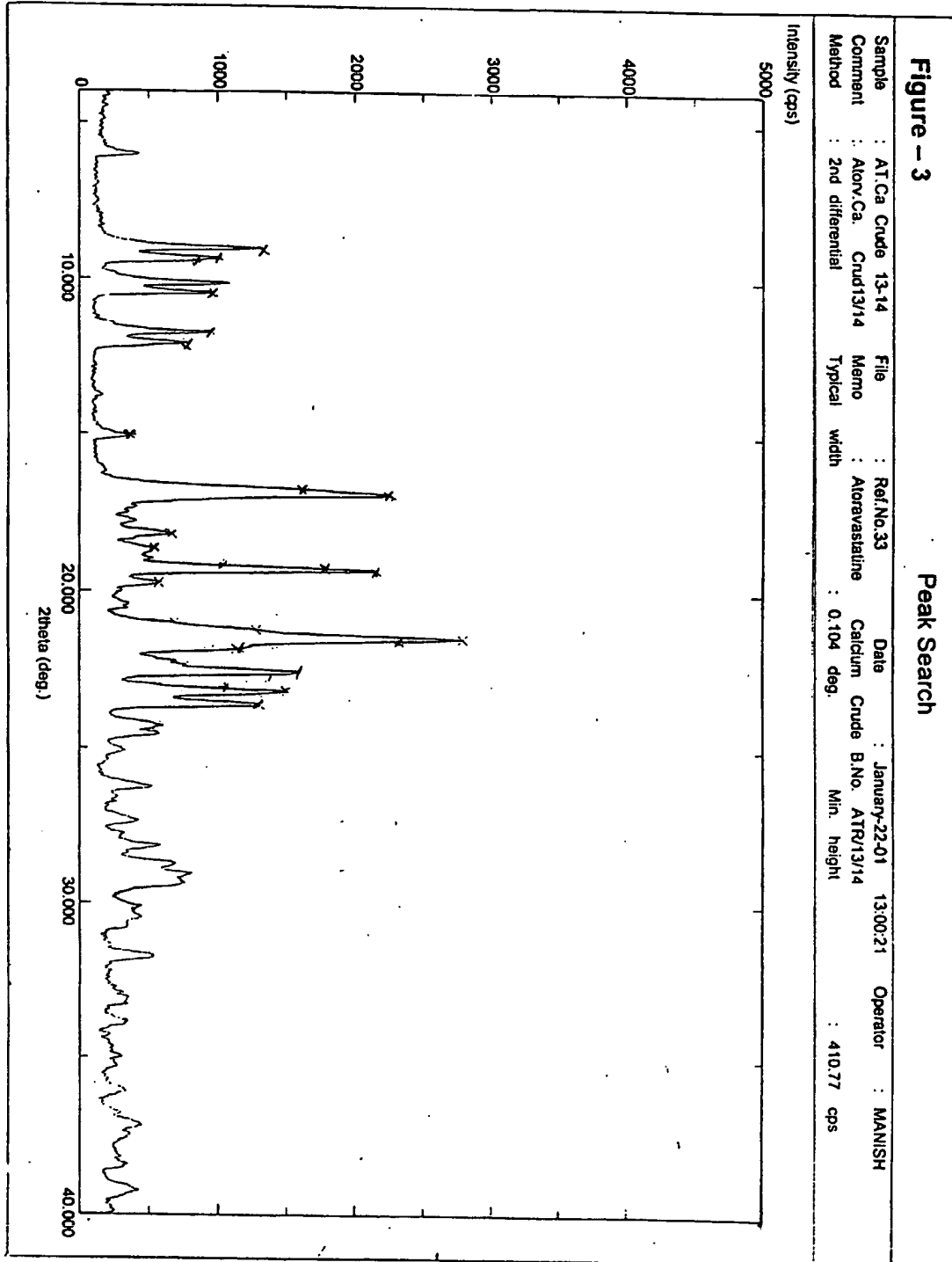
43. The process as claimed in claim 42 wherein the volume of methanolic solution of crude amorphous atorvastatin calcium is 10 times as that of crude amorphous atorvastatin calcium before the methanolic solution is added to water to precipitate pure amorphous atorvastatin calcium.
- 5 44. A process as claimed in claim 1 wherein the amount of water employed for the precipitation of pure amorphous atorvastatin calcium from it's methanolic solution is 1-4 times as that of methanol in volume in purification stage.
45. A process as claimed in claim 44 wherein the amount of water employed
10 for the precipitation of pure amorphous atorvastatin calcium from it's methanolic solution is twice as that of methanol in volume in purification stage.
46. A process as claimed in claims 41,42 and 43 herein said treatment with methanol is carried out at a temperature of 30 to 60°C.
- 15 47. A process as claimed in claim 46 wherein said temperature is 30 to 35°C.
48. A process as claimed in any preceding claim wherein the amount of activated carbon is 2-10% w/w as that of crude amorphous atorvastatin calcium.
49. A process as claimed in claim 48 wherein the amount of activated carbon
20 is 5% w/w as that of crude amorphous atorvastatin calcium.
50. A process as claimed in claims 48 and 49 wherein said treatment with activated carbon is carried out a temperature of 30 to 35°C.
51. A process as claimed in any one of claims 48 and 49 wherein said treatment with activated carbon is carried out for about 15 to 60 minutes.
- 25 52. A process as claimed in claim 50 and 51 wherein said treatment with activated carbon is carried out for about 30 minutes.
53. A process as claimed in claim 1 wherein calcium hydroxide present in crude amorphous atorvastatin calcium is removed in successive purification stage.
- 30 54. A process as claimed in claim 1 wherein the preparation of atorvastatin calcium in amorphous form substantially is described herein with reference to the accompanying examples and drawings.

55. A process as claimed in claim 1 wherein protected diol tert-butyl ester (a) is employed to prepare amorphous atorvastatin calcium.
56. A process as claimed in claim 1 wherein corresponding lactone compound is not employed for the preparation of amorphous atorvastatin calcium.
57. A process as claimed in claim 1 wherein crystalline forms of atorvastatin calcium are not employed for the preparation of amorphous atorvastatin calcium in basic scope of the present invention disclosed herein.
58. A process as claimed in claim 1 wherein crystalline forms of atorvastatin calcium are converted into amorphous atorvastatin calcium as an additional procedure, included in basic scope of the present invention disclosed herein.









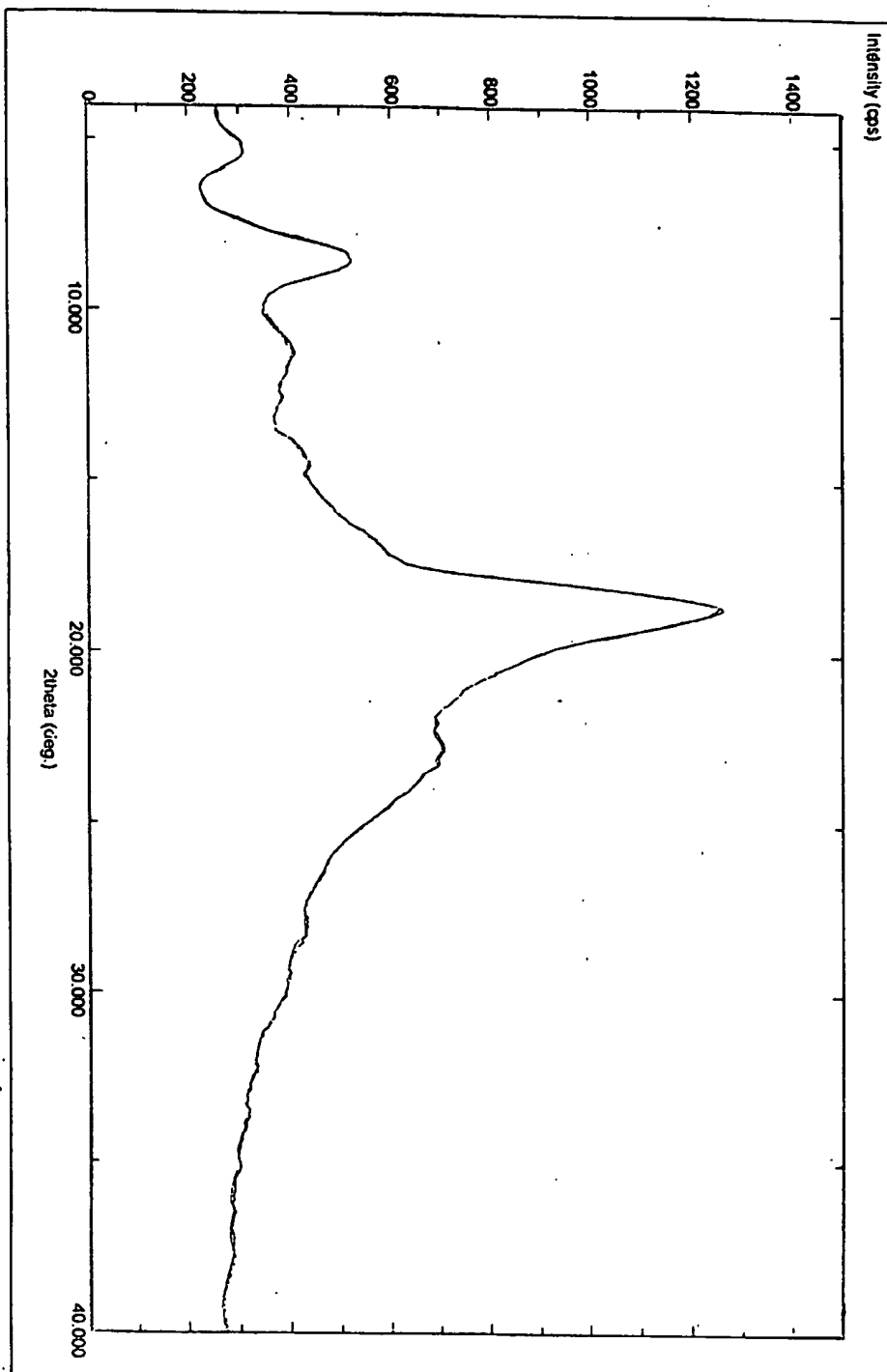
Peak Search

Peak Search													
Sample	AT:Ca	Crude	13-14	File	Ref.No.33	Date	January-22-01	13.00:21	Operator	MANISH			
Comment	Ator:Ca	Crude	13/14	Memo	Atorvastatine	Calcium	Crude	B.No.	ATR/13/14				
Method	2nd differential			Typical	width	0.104	deg.						
Peak no.	2theta	FWHM	d-value	Intensity	I/Io	Peak no.	2theta	Min. height	FWHM	d-value	Intensity	I/Io	
1	9.020	0.129	9.7959	1323	48	31	28.770	0.082	3.1005	672	25		
2	9.320	0.106	9.4812	1027	37	32	29.020	0.153	3.0744	812	30		
3	9.420	0.094	9.3808	844	31	33	29.240	0.059	3.0517	729	27		
4	10.140	0.141	8.7163	1083	39	34	29.340	0.059	3.0416	759	28		
5	10.450	0.141	8.4584	976	35	35	29.430	0.106	3.0325	676	25		
6	11.710	0.106	7.5509	960	35	36	30.090	2.9674	439	16		
7	12.050	0.106	7.3386	782	28	37	30.440	2.9341	435	16		
8	15.030	5.8896	361	13	38	30.760	2.9043	341	13		
9	16.750	0.153	5.2885	1617	58	39	31.700	2.8203	518	18		
10	16.930	0.176	5.2327	2251	81	40	33.290	2.6891	327	12		
11	18.180	0.176	4.8756	669	24	41	33.820	2.6482	340	13		
12	18.650	0.082	4.7538	543	20	42	34.960	2.5644	285	11		
13	19.260	0.059	4.6046	1785	64	43	36.040	2.4900	308	11		
14	19.330	0.141	4.5881	2137	77	44	37.110	2.4206	432	16		
15	19.730	0.200	4.4960	575	21	45	38.390	2.3428	326	12		
16	20.890	0.071	4.2288	688	25	46	39.190	2.2968	385	14		
17	21.210	0.094	4.1855	1280	46								
18	21.460	0.176	4.1373	2797	100								
19	21.530	0.082	4.1240	2325	84								
20	21.830	0.176	4.0680	1132	41								
21	22.200	0.094	4.0010	690	25								
22	22.330	0.071	3.9780	767	28								
23	22.570	0.271	3.9362	1588	57								
24	23.150	0.106	3.8389	1501	54								
25	23.240	0.071	3.8243	1302	47								
26	23.590	0.224	3.7683	1308	47								
27	24.250	0.071	3.6672	606	22								
28	24.500	0.176	3.6304	566	21								
29	28.130	0.129	3.1696	586	21								
30	28.670	0.141	3.1111	670	24								

Figure - 4

Smoothing

Sample name:	AT/Ca Crude 13-17	File	:	Ref/No.34	Date	:	January-22-01	13:52:59	Operator	:	MANISH
Comment	: Alor/Ca. Crude 13/17	Memo	:	Aloravastatine	Calcium	:	Crude B.No. ATR/13/17				
Method	: Averaging	Smoothing Points:	:	99							



INTERNATIONAL SEARCH REPORT

In national Application No

PCT/NL 01/00110

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/34 C07D405/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>BAUMANN K L ET AL: "THE CONVERGENT SYNTHESIS OF CI-981, AN OPTICALLY ACTIVE, HIGHLY POTENT, TISSUE SELECTIVE INHIBITOR OF HMG-COA REDUCTASE" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 33, no. 17, 21 April 1992 (1992-04-21), pages 2283-2284, XP000608147 ISSN: 0040-4039 the whole document</p> <p style="text-align: center;">--- -/--</p>	1-6, 17



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

5 April 2002

Date of mailing of the international search report

15/04/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Seitner, I

INTERNATIONAL SEARCH REPORT

In ——— International Application No

PCT/N 01/00110

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GRAUL A ET AL: "ATORVASTATIN CALCIUM" DRUGS OF THE FUTURE, BARCELONA, ES, vol. 22, no. 9, 1997, pages 956-968, XP000904817 ISSN: 0377-8282 scheme 1, compound (XIX) scheme 2, compounds (XXIV), (XIX) scheme 4, compound (XLIII) ---	1-6,17
X	WO 94 16693 A (WARNER LAMBERT CO) 4 August 1994 (1994-08-04) example A ---	1-6,17
X	US 5 273 995 A (ROTH BRUCE D) 28 December 1993 (1993-12-28) cited in the application scheme 2 example 10 ---	1-6,17
X	WO 97 03960 A (WARNER LAMBERT CO ;LIN MIN (US); SCHWEISS DIETER (US)) 6 February 1997 (1997-02-06) cited in the application claim 1 ---	58
X	WO 00 71116 A (THAPER RAJESH KUMAR ;KUMAR YATENDRA (IN); RANBAXY LAB LTD (IN); KU) 30 November 2000 (2000-11-30) claim 1 ---	58
E	WO 01 42209 A (LEK TOVARNA FARMACEVTSKIH ;PFLAUM ZLATKO (SI)) 14 June 2001 (2001-06-14) claim 1 -----	58

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IN 01/00110

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9416693	A	04-08-1994	AT 178794 T	15-04-1999
			CA 2150372 A1	04-08-1994
			DE 69324504 D1	20-05-1999
			DE 69324504 T2	26-08-1999
			DK 680320 T3	25-10-1999
			EP 0680320 A1	08-11-1995
			ES 2133158 T3	01-09-1999
			GR 3030359 T3	30-09-1999
			JP 8505640 T	18-06-1996
			MX 9400281 A1	29-07-1994
			SG 45369 A1	16-10-1998
			WO 9416693 A1	04-08-1994
			US 5686104 A	11-11-1997
			US 6126971 A	03-10-2000
US 5273995	A	28-12-1993	MX 9203143 A1	01-07-1992
			AT 207896 T	15-11-2001
			AU 628198 B2	10-09-1992
			AU 5972490 A	24-01-1991
			CA 2021546 A1	22-01-1991
			DE 1061073 T1	03-05-2001
			DE 69033840 D1	06-12-2001
			DK 409281 T3	25-02-2002
			EP 1061073 A1	20-12-2000
			EP 0409281 A1	23-01-1991
			ES 2153332 T1	01-03-2001
			FI 94339 B	15-05-1995
			IE 902659 A1	27-02-1991
			JP 3058967 A	14-03-1991
			KR 167101 B1	15-01-1999
			NO 174709 B	14-03-1994
			NO 176096 B	24-10-1994
			NZ 234576 A	23-12-1992
			PT 94778 A , B	20-03-1991
			SG 46495 A1	20-02-1998
			ZA 9005742 A	25-03-1992
WO 9703960	A	06-02-1997	AT 199542 T	15-03-2001
			AU 700794 B2	14-01-1999
			AU 6497896 A	18-02-1997
			BG 102188 A	31-08-1998
			BR 9609714 A	23-02-1999
			CA 2220455 A1	06-02-1997
			CN 1190956 A	19-08-1998
			CZ 9800122 A3	16-12-1998
			DE 69611999 D1	12-04-2001
			DE 69611999 T2	26-07-2001
			DK 839132 T3	09-04-2001
			EE 9700369 A	15-06-1998
			EP 0839132 A1	06-05-1998
			ES 2156997 T3	01-08-2001
			HR 960312 A1	28-02-1998
			HU 220343 B	28-12-2001
			IL 122161 A	14-07-1999
			JP 11510486 T	14-09-1999
			NO 980209 A	16-01-1998
			PL 324463 A1	25-05-1998
			PT 839132 T	29-06-2001

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IN 01/00110

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9703960	A	SI 839132 T1 SK 5898 A3 WO 9703960 A1 US 6274740 B1	30-06-2001 05-08-1998 06-02-1997 14-08-2001
WO 0071116	A 30-11-2000	AU 1996700 A EP 1185264 A1 WO 0071116 A1	12-12-2000 13-03-2002 30-11-2000
WO 0142209	A 14-06-2001	SI 20425 A AU 1543801 A WO 0142209 A1	30-06-2001 18-06-2001 14-06-2001